Depression phenotype, inflammation and the brain: Implications for future research.

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Abstract

Inflammation is implicated in the etiology of Major Depressive Disorder (MDD). Human neuroimaging techniques are increasingly used to characterize the neural circuitry mediating actions of inflammation on mood, motivation and cognition and its relationship to MDD. In this issue, Byrne and colleagues report the first systematic review of these studies. The systematic review provides a much-needed synthesis of current research findings and highlights the role of cortical and subcortical brain structure and function. In this accompanying commentary, we highlight further points of particular relevance to future studies, including the potential advantages of functional phenotype models rather than the emphasis on mutually exclusive diagnostic categories in describing MDD and other psychiatric disorders. Novel imaging techniques will further enhance possibilities to clarify the link between inflammation and depression. New research challenges are described regarding the relationships between behavioural phenotype, brain structure and function, and peripheral inflammation.

Major Depressive Disorder (MDD) is one of the leading causes of disability worldwide and significantly worsens prognosis and quality of life for people with comorbid physical disorders. Yet despite this major global burden, advances in understanding MDD pathogenesis have been slow, and translational breakthroughs disappointingly rare. Over the past two decades a surge of research has focused on understanding the role of inflammation in major mental illnesses. In MDD, characteristic alterations in serum cytokines, chemokines and acute phase reactant protein concentrations have been confirmed in at least 4 recent meta-analyses (1-4). Furthermore, longitudinal studies suggest that inflammatory changes predate and likely contribute to the development of depressive symptoms (5); findings that accord with the observation that 1 in 4 patients treated with Interferon-alpha (for hepatitis-C) develop MDD. These studies challenge the long held view of the brain as an 'immune privileged site'. By characterizing the bi-directional interactions between physiological stress responses, immune/inflammatory pathways and the brain, they are also beginning to offer a coherent neurobiological framework for understanding this multi-componential disorder (6, 7). This framework additionally offers the prospect of identifying circulating inflammatory biomarkers for treatment response, and novel anti-inflammatory agents as adjunctive therapies for treatment resistance (8, 9).

While preclinical studies have helped clarify actions of systemic inflammation on regional brain structure and function, the use of advanced brain imaging techniques to explore similar relationships in clinical studies remains in a fledgling state.

In the current issue of Psychosomatic Medicine, Byrne and colleagues report the first systematic review of studies using brain imaging to characterize the neural mechanisms linking inflammation and depressive symptoms (10). They reviewed 26 studies that report effects of both experimentally induced inflammation and inflammation in the context of MDD and identify a cluster of subcortical (basal ganglia, ventral striatum, hippocampus,

hypothalamus and amygdala) and cortical (insula, anterior cingulate, orbitofrontal, ventromedial, and dorsolateral prefrontal cortices) structures that appear central to effects of inflammation on mood and depressive symptomatology. This review provides a much-needed synthesis of current research findings, highlights caveats of the existing literature and points towards potential pathways for future research. In this editorial, we highlight issues that will need to be addressed in future studies exploring relationships between behavioural phenotype, brain and peripheral inflammation, and examine how refining these measurements will be crucial to further progress.

Measuring the right phenotype:

While most studies find a relationship between inflammation and MDD, it is important to note that a significant proportion of people with MDD do not show raised inflammatory markers. Furthermore, immune/inflammatory disruption is also found in a number of other psychiatric conditions, including schizophrenia and PTSD (11, 12). Inflammation is therefore neither necessary nor specific to MDD. Complicating this further, we know that depressive symptoms are not limited to MDD, but instead are common in patients diagnosed with a range of other illnesses including anxiety disorders and psychosis. This highlights the highly heterogeneous nature of current psychiatric diagnostic categories (13) which frequently share overlapping symptomatology, genetic and biological susceptibility (14) and likely mitigates success of attempts to map diagnoses to specific alterations in brain structure/function. This problem is widely acknowledged across psychiatric research and has led to the recognition that a categorical (diagnostic criteria based) approach may be impeding biologically relevant translational research (15). In keeping with this, there is a move to replace existing categorical models of mental illnesses, with trans-diagnostic dimensional models that incorporate genes, biology and cognitive neuroscience (16). There is also a move towards

implementing computational models of psychiatric symptomatology that may better map complex cognitive and behavioural constructs at the neuronal level (17). Therefore, rather than exploring associations within specific illness categories, future research may need to look at associations between inflammation and research domains or computational models of complex cognitive/ behavioural functions.

Measuring the brain:

Neuroimaging is a fast evolving field. While traditional neuroimaging approaches have examined how measured variables (cognitive function/ inflammatory markers) are correlated with patterns of activation, volume or metabolism on a region-by-region basis, more recent studies have focused on "how" these processes are implemented and distributed across brain regions using advanced computational modelling. The latter approaches are enabling us to better understand how networks of regions interact together to support complex behaviors.

By regressing variables derived from competing computational models of a specific cognitive function, model-based approaches to fMRI provide insight into ‘how’ rather than simply ‘where’ a particular cognitive process is implemented within the brain. This approach also has the potential to provide a more fine-grained understanding of brain responses to inflammation. For example, in their review, Byrne et al. identify the ventral striatum and insula as key brain regions sensitive to systemic inflammation. Using a reinforcement-learning model, Harrison et al. deconstruct the concept of 'motivational reorientation', a core feature of inflammation induced sickness-behavior, to show that experimentally induced inflammation significantly enhances sensitivity to punishments versus rewards (18). Furthermore, they showed that prediction error (PE) signals (difference between

expected and obtained reward/punishment) believed to guide learning were significantly modulated by inflammation, with inflammation prompting a significant reduction in ventral striatal encoding of reward PE and a converse enhancement of insula encoding of punishment PE. Model-based studies such as this will be essential to future attempts to understand how inflammation alters specific neural computational mechanisms that lead to observed changes in behavior.

A second approach gaining increasing importance is the use of resting state fMRI to explore how dynamically interacting core intrinsic connectivity networks (ICN), are altered by inflammatory stimuli. For example, Felger et al. recently showed an inverse association between circulating C-reactive protein (CRP) levels and striatal functional connectivity in MDD (19). Other key substrates identified by Byrne et al. include the anterior insula and anterior cingulate cortices. These regions are noteworthy as they both form key nodes of the salience network (SN) implicated in allocating attentional resources to behaviorally relevant external and internal stimuli (20-22). Furthermore, internal (interoceptive) signals from the body are postulated to have a primary 'viscero-cortical' representation within the SN. Inflammatory mediators, are known to activate vagal afferents and the sensory circumventricular organs as well as the brainstem ‘viscerosensory hub’ evoking visceral reflexes and subjective experiences of fatigue, malaise, and anorexia (21, 23). Further upstream, involvement of the SN may also be associated with aberrant salience mapping (24). The centrality of the insula to autonomic, interoceptive, and viscero-cortical representation, together with its role in ‘switching’ between brain states, make it an ideal candidate for investigating how interoceptive inflammatory signals modulate complex neurocognitive function.

Resting state fMRI has also been used to explore effects of inflammation on global network function using graph theoretical metrics derived from complex network analysis (CNA). Using CNA of resting state BOLD cross-correlations Dipasquale et al. have recently shown that peripherally administered IFN-α rapidly reduces global network connectivity and network efficiency indicating a global reduction in information transfer among nodes forming the whole brain network (25). Similar data-driven approaches could include investigating how inflammation affects the regional homogeneity (ReHo) of BOLD signals, a measure shown to be disrupted in a regionally specific manner in MDD (26). In this regard, Byrne et al. found evidence to support effects of inflammation on glutamatergic activity (10). Measures such as the amplitude of low frequency fluctuations (alFF) may be a useful index to further quantify how these inflammation-induced changes in glutamatergic function relate to observed alterations in BOLD fluctuations at rest (27). Finally, newer MRI based sequences like quantitative magnetization transfer (qMT), neurite orientation dispersion and density imaging (NODDI) and free water imaging also appear to be promising approaches for characterizing effects of inflammation on brain pathophysiology (28-30). Future studies are likely to see increasing use of these complimentary imaging technologies to understand how inflammation-induced changes in brain microstructure relate to associated changes in function.

Measuring inflammatory markers:

Three points appear crucial when measuring inflammatory markers. Firstly, it is essential to dissect effects of 'non-sterile' inflammation (induced by infection/experimental cytokines/vaccines/endotoxins) from inflammation secondary to 'sterile' stressors e.g. psychological stress (31) and furthermore recognize that not all ‘non-sterile’ challenges recruit the same signal transduction pathways (32). Although there is increasing evidence for

"inflammasome" activation and aggregation in response to both sterile and non-sterile inflammation, these effects still need to be qualified and quantified (33, 34). Similarly, while experimental induction of inflammation may help quantify effects of inflammation in the absence of confounding factors, in real life this is rarely the case. For example, previous studies have illustrated how inflammatory markers may mediate the relationship between socioeconomic status and grey/ white matter structure (35-37). However, it remains unclear whether inflammatory pathways linking real-life sustained stressful conditions to the brain differ from those associated with experimentally induced inflammation.

Secondly, it remains unclear to what extent circulating inflammatory markers reflect central levels. While most of the studies reviewed by Byrne and colleagues examined associations between circulating inflammatory markers and brain structure/ function, few measured central inflammatory markers. In this regard it is interesting to note that Haroon et al., recently found a high correlation between plasma and cerebrospinal fluid (CSF) CRP, yet only plasma measures correlated with basal ganglia glutamate (38). Other studies have found no relationship between circulating and CSF inflammatory markers (39, 40). Measuring CSF/central inflammation is further complicated by the presence of both soluble and cell bound cytokines fractions in the brain. For example, microglial activity produces predominantly bound tumor necrosis factor (TNF) that is difficult to measure (39). Moreover, there has not been a consistent relationship between CSF inflammatory markers and MDD (40-42). Some studies have used 18nDa translocator protein (TSPO) Positron Emission Tomography (PET) which is expressed on activated microglia to quantify central inflammation. In an interesting recent study, Sandiego et al. showed that endotoxin challenge in healthy adults results in rapid and widespread microglial activation throughout the brain (43). However, findings using TSPO binding in MDD have been mixed (10). Furthermore, TSPO PET studies are not without their own difficulties. TSPO PET is expensive, existing

TSPO ligands like [^{11}C]PK11195 have poor signal to noise ratio and newer tracers like [^{11}C]PBR28 show marked between subject variations in binding affinity (44). Additionally, not all microglia express TSPO, and TSPO PET cannot differentiate an increase in microglial number from an increase in TSPO expression within each microglia (44).

A third issue is identifying what markers of inflammation should we be measuring. Most research to date has focused on investigating relationships between pro-inflammatory cytokines and psychiatric illnesses. Similarly, most of the studies cited by Byrne et al. only measured cytokines identified by the meta-analyses linking inflammation to depression (4). Here, the underlying assumption is that excess pro-inflammatory cytokines are harmful to the brain. However, it is clear that some pro-inflammatory cytokines such as TNF are required for healthy CNS function (45). While a simple division between pro-and anti-inflammatory cytokines may be artificial, a balance between different inflammatory markers clearly exists within the body. Furthermore, chemokines and colony-stimulating factors have also been linked to cognitive dysfunction and the pathophysiology of psychiatric symptom clusters (46). Given the complex interplay between these factors sophisticated modeling using techniques such as principal component analysis, hierarchical or other advanced clustering techniques are likely to be required to fully capture how changes in networks of interacting inflammatory markers act on the brain to induce associated changes in behavior and cognition (47).

To conclude, raised inflammatory markers have been associated with a number of psychiatric conditions including depression and may indeed play an etiological role in these disorders. Inflammation may perhaps be better conceptualized as a generalized physiological (or pathological) response to a stressor (sterile or non-sterile) that triggers a cascade of events that affect core information processing systems in the brain, leading ultimately to a discrete

behavioural phenotype (e.g. anhedonia / motivational reorientation) that spans diagnostic categories. Although the key mechanisms linking inflammatory factors to the human brain are gradually being established, future work will need to focus on refining peripheral immune measures. These research findings, together with the application of advanced brain-imaging techniques, should help us to move closer to the goal of understanding more precisely the relationship between peripheral inflammation, regional brain structure / function and associated changes in discrete clinical and cognitive phenotypes.

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